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Lysoplasmenylethanolamine accumulation in ischemic/reperfused isolated fatty acid-perfused hearts.

Davies NJ, Schulz R, Olley PM, Strynadka KD, Panas DL, Lopaschuk GD.

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Lysophospholipid accumulation has been implicated in the pathogenesis of irreversible injury during myocardial ischemia and reperfusion. Plasmalogens (phospholipids with a vinyl-ether bond in the sn-1 position) account for more than 50% of total myocardial sarcolemmal and sarcoplasmic reticulum phospholipids. Accumulation of plasmalogen choline and ethanolamine lysophospholipids (lysoplasmenylcholine and lysoplasmenylethanolamine) or the effects of exogenous fatty acids on lysoplasmalogen accumulation during ischemia and reperfusion have not been examined. Isolated working rat hearts perfused with buffer containing either 11 mM glucose or 11 mM glucose plus 1.2 mM palmitate were subjected to aerobic, ischemic, or ischemia/reperfusion protocols. Levels of lysoplasmenylcholine and lysoplasmenylethanolamine were quantified using a two-stage high-performance liquid chromatographic technique. In hearts perfused with glucose alone, no significant differences in levels of lysoplasmenylcholine or lysoplasmenylethanolamine were seen during ischemia or reperfusion. In fatty acid-perfused hearts, however, significant accumulation of lysoplasmenylethanolamine occurred during reperfusion but not during ischemia (723 +/- 112, 734 +/- 83, and 1,394 +/- 193 nmol/g dry wt for aerobic, ischemic, and ischemic/reperfused hearts, respectively; p less than 0.05 for ischemic/reperfused hearts versus aerobic or ischemic hearts). Lysoplasmenylcholine levels after ischemia and reperfusion did not differ significantly from aerobic values, regardless of whether fatty acids were present or absent from the perfusate. Aerobic and ischemic/reperfused rabbit hearts, in the presence of fatty acid, showed a similar profile in their lysoplasmalogen content. We conclude that differential lysoplasmenylethanolamine accumulation occurs during myocardial reperfusion when exogenous fatty acid concentrations are high. This may reflect the selective action of fatty acid intermediates on the metabolism of lysoplasmenylethanolamines.(ABSTRACT TRUNCATED AT 250 WORDS)

PMID: 1576737 [PubMed - indexed for MEDLINE]

1: Circ Res 1998 Sep 7;83(5):533-40

Plasmalogen-derived lysolipid induces a depolarizing cation current in rabbit ventricular myocytes.

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Plasmalogen rather than diacyl phospholipids are the preferred substrate for the cardiac phospholipase A2 (PLA2) isoform activated during ischemia. The diacyl metabolite, lysophosphatidylcholine, is arrhythmogenic, but the effects of the plasmalogen metabolite, lysoplasmenylcholine (LPLC), are essentially unknown. We found that 2.5 and 5 micromol/L LPLC induced spontaneous contractions of intact isolated rabbit ventricular myocytes (median times, 27.4 and 16.4 minutes, respectively) significantly faster than lysophosphatidylcholine (>60 and 37.8 minutes, respectively). Whole-cell recordings revealed that LPLC depolarized the resting membrane potential from -83.5+/-0.2 to -21.5+/-1.0 mV. Depolarization was due to a guanidinium toxin-insensitive Na+ influx. The LPLC-induced current reversed at -18.5+/-0.9 mV and was shifted 26.7+/-4.2 mV negative by a 10-fold reduction of bath Na+ (Na+/K+ permeability ratio, approximately 0.12+/-0.06). In contrast, block of Ca2+ channels with Cd2+ and reducing bath Cl failed to affect the current. The actions of LPLC were opposed by lanthanides. Gd3+ and La3+ were equally effective inhibitors of the LPLC-induced current and equally delayed the onset of spontaneous contractions. However, the characteristics of lanthanide block imply that Gd3+-sensitive, poorly selective, stretch-activated channels were not involved. Instead, the data are consistent with the view that lanthanides increase phospholipid ordering and may thereby oppose membrane perturbations caused by LPLC. Plasmalogens constitute a significant fraction of cardiac sarcolemmal choline phospholipids. In light of their subclass-specific catabolism by phospholipase A2 and the present results, it is suggested that LPLC accumulation may contribute to ventricular dysrhythmias during ischemia.

PMID: 9734476 [PubMed - indexed for MEDLINE]

1: J Mol Cell Cardiol 1987 Oct;19 Suppl 5:45-53 Related Articles, Links

Lysophosphoglycerides and ventricular fibrillation early after onset of ischemia.

Corr PB, Yamada KA, Creer MH, Sharma AD, Sobel BE.

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Lysophosphoglycerides accumulate in ischemic myocardium and induce electrophysiologic alterations in normoxic tissue in vitro closely analogous to those seen during ischemia in vivo. The present study was performed to define the temporal alterations of myocardial phospholipids during the first 3 minutes of ischemia in anesthetized cats and to determine whether the magnitude of the increase in lysophosphoglycerides correlates with the severity of ventricular arrhythmias. Fast-frozen transmural biopsies were obtained simultaneously from the ischemic and non-ischemic zones of the left ventricle. In control animals, values of lysophosphatidylcholine (LPC) did not differ in anterior (2.1 +/- 0.2 nmol/mg protein) compared with lateral (2.2 +/- 0.2 nmol/mg protein) regions of the left ventricular wall. The values for LPC in the anterior and lateral regions were also identical when expressed as % of total phospholipid phosphorus (1.4 +/- 0.1%). Comparing these values to those of all other animals biopsied within 3 minutes of ischemia, no significant increase in LPC was seen (1.7 +/- 0.2%). However, stratification of the animals based on the severity of ventricular arrhythmias showed striking differences. In animals without arrhythmias, no significant change occurred in LPC (1.2 +/- 0.2% phospholipid phosphorus or 2.0 +/- 0.3 nmol/mg protein) compared with the non-ischemic tissue control values (1.4 +/- 0.1% phospholipid phosphorus or 2.1 +/- 0.2 nmol/mg protein). In contrast, in animals with arrhythmias, a striking and significant increase in LPC (to 2.0 +/- 0.2% phospholipid phosphorus or 3.1 +/- 0.3 nmol/mg protein) was seen.(ABSTRACT TRUNCATED AT 250 WORDS)

PMID: 3430644 [PubMed - indexed for MEDLINE]

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☐ 1: Coron Artery Dis 1997 Jan;8(1):19-27

Time course of lysophosphatidylcholine release from ischemic human myocardium parallels the time course of early ischemic ventricular arrhythmia.

Sedlis SP, Hom M, Sequeira JM, Tritel M, Gindea A, Ladenson JH, Jaffe AS, Esposito R.

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BACKGROUND: We determined the kinetics of the release of lysophosphatidylcholine (LPC) into the coronary sinus of patients undergoing stress tests after coronary artery bypass grafting. The kinetics were consistent with a role for this amphiphile in the pathogenesis of ischemic ventricular arrhythmia, a major cause of sudden death. METHODS: Stress testing was initiated in the operating suite by pacing at a rate of 160 beats/min for 2 min. Ischemia was then induced by clamping the bypass grafts to the anterior wall for a maximal time of 4 min. RESULTS: The pacing procedure induced a prompt but reversible increase in coronary sinus LPC concentration from a baseline of 60.9 +/- 2.5 to 83.8 +/- 5.0 mumol/l via pacing alone, and a further increase to 101.8 +/- 6.7 mumol/l when the grafts were clamped for 2 min ($P < 0.01$). Six minutes after the cessation of pacing, LPC concentration returned to 67.5 +/- 4.4 mumol/l. CONCLUSIONS: These results demonstrate that severe myocardial ischemia is an agonist for rapid release of LPC from the myocardium. Kinetics of this release paralleled the time-course of early onset of electrophysiologic changes in isolated myocytes and perfused heart preparations in vitro. These results indicate that LPC may have an important role in the pathogenesis of ischemic ventricular arrhythmia in patients.

PMID: 9101118 [PubMed - indexed for MEDLINE]

1: Lipids 1988 Jan;23(1):32-5

Lysophosphatidylcholine accumulation in the ischemic canine heart.

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The production of cardiac arrhythmias and the elevation of lysophosphatidylcholine level in the ischemic myocardium have been well-documented in a number of studies. However, the relationship between the production arrhythmias and the elevation of tissue lysophosphatidylcholine level was not reported. In this study, the lysophosphatidylcholine level and the occurrence of cardiac arrhythmias in the ischemic canine heart were monitored. A temporal relationship between the accumulation of lysophosphatidylcholine and the occurrence of arrhythmias was established after five hr of ischemia. A significant elevation of lysophosphatidylcholine was detected at three hr of ischemia without the occurrence of arrhythmias. The results indicate that cardiac arrhythmias did not cause the elevation of lysophosphatidylcholine and if lysophospholipids are causally related to the arrhythmias that a critical level of the lysophospholipid must accumulate in order to elicit electrophysiological alterations.

PMID: 3352470 [PubMed - indexed for MEDLINE]

1: Fed Proc 1983 May 15;42(8):2454-9

Arrhythmogenic properties of phospholipid metabolites associated with myocardial ischemia.

Corr PB, Sobel BE.

Several observations suggest that the accumulation of metabolites within ischemic regions may contribute to the electrophysiological derangements characteristic of ischemic myocardium. We, and more recently others, have detected an increase in lysophosphoglycerides (LPGs) in ischemic tissue in vivo as well as in effluents from ischemic regions. At comparable concentrations, LPGs induce electrophysiological alterations in vitro analogous to changes seen in vivo with ischemia. Experiments with [14C]lysophosphatidylcholine indicated that incorporation comprising less than 1% of total cellular phospholipid is sufficient to induce electrophysiological derangements in isolated ventricular muscle. Reduction of pH to 6.7, analogous to the fall seen within minutes in ischemic tissue in vivo, potentiates the electrophysiological actions markedly without increasing membrane incorporation. In recent studies the activity of enzymes potentially responsible for the accumulation of LPGs during ischemia has been found to be altered by concomitants of ischemia, including increased concentrations of H+ and long-chain acyl carnitine. Thus, accumulation of LPGs and related compounds may contribute substantially to induction of electrophysiological derangements accompanying ischemia and may be amenable to therapeutic manipulation designed to alleviate malignant ventricular dysrhythmia.

PMID: 6840297 [PubMed - indexed for MEDLINE]

1: J Lab Clin Med 1993 Jan;121(1):111-7 Related Articles, Links

Lysophosphatidylcholine accumulation in ischemic human myocardium.

Sedlis SP, Hom M, Sequeira JM, Esposito R.

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Lysophosphatidylcholine accumulates in the coronary sinus during pacing-induced myocardial ischemia in humans. This amphiphile accelerates Ca++ flux leading to cell injury in cultured cardiac myocytes, but it is not known whether lysophosphatidylcholine accumulation is injurious to human myocardium. In this study, we measured lysophosphatidylcholine in normal human myocardium obtained during cardiac surgery and exposed to ischemic conditions in vitro. Total lysophosphatidylcholine concentration (sum of lysophosphatidylcholine remaining in tissue and lysophosphatidylcholine released into the buffer) increased from 0.73 +/- 0.08 nmol/mg protein at baseline to 1.83 +/- 0.45 nmol/mg protein after 5 minutes of ischemia ($p < 0.001$), and was associated with evidence of cell injury (26% depletion of tissue lactate dehydrogenase). Significant lysophosphatidylcholine release into the incubation buffer (0.41 +/- 0.11 nmol/mg protein) also occurred after 5 minutes of ischemia. In contrast, there was no lysophosphatidylcholine accumulation or release and no lactate dehydrogenase depletion in oxygenated and perfused controls. Attenuation of lysophosphatidylcholine accumulation by incubation with lysophospholipase did not prevent cell injury. Lysoplasmalogen was not detected in ischemic tissue. We conclude that lysophosphatidylcholine accumulation is a marker of myocardial ischemia in humans.

PMID: 8426072 [PubMed - indexed for MEDLINE]

☐ 1: J Clin Invest 1986 Jul;78(1):271-80

Electrophysiologic effects of intracellular lysophosphoglycerides and their accumulation in cardiac lymph with myocardial ischemia in dogs.

Akita H, Creer MH, Yamada KA, Sobel BE, Corr PB.

Lysophosphatidylcholine (LPC) accumulates in ischemic tissue, and exogenous LPC (20-100 microM) induces electrophysiologic alterations in vitro. However, to determine whether compartmentalization is critical, intracellular pressure microinjection of LPC was performed with simultaneous recording of the transmembrane action potential. Intracellular LPC in concentrations as high as 500 microM (n = 18), calculated based on calibration of injectate volume and cellular volume, did not induce electrophysiologic alterations. The concentrations and efflux of phospholipids and lysophospholipids were assessed in lymph obtained from the supracardiac lymph vessel in anesthetized dogs to assess the extent of extracellular accumulation. Prior to ischemia, phosphatidylcholine (PC) was the major phospholipid in lymph (79 +/- 2%) with substantial quantities of sphingomyelin (11 +/- 2%) and LPC (6 +/- 1%). With ischemia, the concentration of LPC increased by 18%, and net efflux of LPC increased by 24% (P less than 0.01) with no net efflux of PC or other assayed phospholipids. The calculated concentration of LPC increased from 84 to 197 microM in lymph within the ischemic region, a concentration sufficient to induce electrophysiologic derangements.

PMID: 3013938 [PubMed - indexed for MEDLINE]